Date of Approval: August 8, 2018

FREEDOM OF INFORMATION SUMMARY

SUPPLEMENTAL NEW ANIMAL DRUG APPLICATION

NADA 141-439

Inteprity™

avilamycin Type A medicated article

Type A medicated article to be used in the manufacture of Type C medicated feeds

Broiler chickens

To change the broiler chicken age restriction caution statement from 10 days to 18 days as follows: To assure responsible antimicrobial drug use in broiler chickens, treatment administration must begin on or before 18 days of age.

Sponsored by:

Elanco US Inc.

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I. GENERAL INFORMATION

A. File Number

NADA 141-439

B. Sponsor

Elanco US Inc.
2500 Innovation Way
Greenfield, IN 46140

Drug Labeler Code: 058198

C. Proprietary Name

Inteprity™

D. Product Established Name

Avilamycin Type A medicated article

E. Pharmacological Category

Antimicrobial

F. Dosage Form

Type A medicated article to be used in the manufacture of Type C medicated feeds

G. Amount of Active Ingredient

45.4 g/lb (100 g/kg)

H. How Supplied

25 kg (55.12 lb) bag

I. Dispensing Status

VFD

J. Dosage Regimen

Feed at 13.6 to 40.9 grams per ton of Type C medicated feed (15 to 45 ppm) as the sole ration for 21 consecutive days.

K. Route of Administration

Oral

L. Species/Class

Broiler chickens

M. Indication

For the prevention of mortality caused by necrotic enteritis associated with *Clostridium perfringens* in broiler chickens.

N. Effect of Supplement

This supplement provides for a change in the broiler chicken age restriction caution statement from 10 days to 18 days as follows: To assure responsible antimicrobial drug use in broiler chickens, treatment administration must begin on or before 18 days of age.

II. EFFECTIVENESS

A. Dosage Characterization

This supplemental approval does not change the previously approved dosage range. The Freedom of Information (FOI) Summary for the original approval of NADA 141-439 dated May 2, 2016, contains dosage characterization information for broiler chickens.

B. Substantial Evidence

CVM did not require effectiveness studies for this supplemental approval. The FOI Summary for the original approval of NADA 141-439 dated May 2, 2016, contains a summary of studies that demonstrate effectiveness of the drug for the prevention of mortality caused by necrotic enteritis associated with *C. perfringens* in broiler chickens.

III. TARGET ANIMAL SAFETY

CVM did not require target animal safety studies for this supplemental approval. The FOI Summary for the original approval of NADA 141-439 dated May 2, 2016, contains a summary of target animal safety studies for broiler chickens.

IV. HUMAN FOOD SAFETY

A. Antimicrobial Resistance

The Agency evaluated microbial food safety information to support a label change to allow for the administration of avilamycin to chickens beginning at 18 days of age or less. Avilamycin belongs to the orthosomycin class of antimicrobials and at this time, there are no orthosomycin drug products approved for use in humans in the United States. For this label change, the firm provided information to the Agency in the form of a microbial food safety *hazard characterization*. The *hazard characterization* included information on avilamycin - specifically its spectrum of antibacterial activity, mechanism(s) of avilamycin resistance, and impact on the development or selection of antimicrobial resistance among foodborne pathogens of public health concern (*Enterococcus* and *Campylobacter*) in or on broiler chickens following their treatment with avilamycin.

The *hazard characterization* demonstrated that 1) avilamycin selects for avilamycin resistance in both *Enterococcus* and *Campylobacter,* but orthosomycin antimicrobials are not considered to be medically important, and 2) that

resistance to avilamycin does not select for cross-resistance to macrolides, and to date there are no reports of plasmid-mediated resistance to avilamycin that could result in the co-selection of resistance to other medically important antimicrobials in the United States.

Thus, given the approved conditions of use, including appropriate use parameters to determine if broiler chickens are eligible to receive avilamycin for the prevention of mortality caused by necrotic enteritis associated with *Clostridium perfringens*, the Agency concludes that antimicrobial resistance concerns for orthosomycin-resistant *Campylobacter* and *Enterococcus* originating from avilamycin-treated broiler chickens are minimal.

Based upon this evaluation and the following antimicrobial resistance risk mitigating factors:

- Avilamycin is indicated for, "*For the prevention of mortality caused by necrotic enteritis associated with Clostridium perfringens in broiler chickens",*
- Avilamycin will be available as a veterinary feed directive (VFD), and therefore will be administered under veterinary oversight,
- Avilamycin will be administered for 21 days with the option of no refills, and
- Avilamycin will be administered to chickens starting on or before 18 days of age,

the Agency concludes that the use of avilamycin, starting on or before 18 days of age, for the prevention of mortality caused by necrotic enteritis associated with *Clostridium perfringens* in broiler chickens, will not result in a significant risk to public health with respect to development of orthosomycin resistance among foodborne *Campylobacter* and *Enterococcus* originating from avilamycin-treated chickens.

B. Effects of Residues on Human Intestinal Flora

CVM did not require additional information on the effects of residues on human intestinal flora for this supplemental approval. The FOI Summary for the original approval of NADA 141-438 dated May 8, 2015, contains a summary of all information used to assess the effects of residues on human intestinal flora.

C. Toxicology

Reassessment of the toxicological acceptable daily intake (ADI) was not needed for this supplemental approval. The FOI Summary for the original approval of NADA 141-438, dated May 8, 2015, contains a summary of all toxicology studies and information.

D. Establishment of the Final ADI

The final ADI is the toxicological ADI of 1.1 mg/kg body weight (bw)/day for total residues of avilamycin derived from the 104-week oral carcinogenicity study in rats. The codified ADI is listed under 21 CFR 556.68.

E. Safe Concentrations for Total Residues in Edible Tissues

Reassessment of the safe concentrations for total residues of avilamycin were not needed for this approval. The safe concentrations of total residues of avilamycin in individual edible tissues of broiler chickens are 220 ppm for muscle, 660 ppm for liver, 1320 ppm for kidney, and 1320 ppm for fat.

F. Residue Chemistry

CVM did not require residue chemistry studies for this supplemental approval. The FOI Summary for the original approval of NADA 141-439 dated May 2, 2016, contains a summary of residue chemistry studies for broiler chickens.

G. Analytical Method for Residues

As indicated in the FOI Summary for the original approval of NADA 141-439, dated May 2, 2016, because a tolerance has not been assigned, a validated analytical method is not necessary.

V. USER SAFETY

The product labeling contains the following information regarding safety to humans handling, administering, or exposed to Inteprity™:

Avilamycin may be irritating to the eyes and may cause allergic reactions in those hypersensitive to avilamycin. Avoid inhalation, oral exposure, and direct contact with skin or eyes. Operators mixing and handling Inteprity Type A medicated article should use protective clothing, impervious gloves, goggles, and an approved dust mask. Wash thoroughly with soap and water after handling. If accidental eye contact occurs, immediately rinse thoroughly with water and seek medical attention. If wearing contact lenses, rinse the eyes first, then remove contact lenses and continue to rinse the eyes thoroughly and seek medical attention. If accidental skin contact occurs, wash all exposed areas of skin with soap and water, and seek medical attention if irritation develops. If accidental inhalation occurs, seek medical attention if breathing difficulty occurs. Not for human consumption. If accidental ingestion occurs, call a physician or poison control center. Do not induce vomiting. Keep out of reach of children. The Safety Data Sheet contains more detailed occupational safety information. To report adverse effects in users, to obtain more information, or to obtain a Safety Data Sheet, call 1-800-428-4441.

VI. AGENCY CONCLUSIONS

The data submitted in support of this NADA satisfy the requirements of section 512 of the Federal Food, Drug, and Cosmetic Act (FD&C Act) and 21 CFR part 514. The data demonstrate that Inteprity™, when used according to the label, is safe and effective for the prevention of mortality caused by necrotic enteritis associated with *C. perfringens* in broiler chickens. Additionally, data demonstrate that residues in food products derived from species treated with Inteprity™ will not represent a public health concern when the product is used according to the label.

A. Marketing Status

A valid veterinary feed directive (VFD) is required to dispense this drug. Any animal feed bearing or containing this drug will be fed to animals only by or on a

lawful VFD issued by a licensed veterinarian in the course of their professional practice. In addition, the VFDs issued for this drug are not refillable.

The decision to restrict this drug to use by or upon a lawful VFD issued by a licensed veterinarian was made because adequate directions cannot be written to enable lay persons to appropriately diagnose and subsequently use this drug product. Use by or on the order of a licensed veterinarian is critical for assuring the safe and appropriate use of this drug product in animals to minimize any potential for the development of bacterial resistance to antimicrobial drugs, and to ensure that edible tissue derived from animals treated with this drug product is safe with regards to human consumption.

B. Exclusivity

This supplemental approval for Inteprity™ qualifies for THREE years of marketing exclusivity under section 512(c)(2)(F)(iii) of the FD&C Act because the supplemental application included safety studies. This exclusivity begins as of the date of our approval letter and only applies to the change in the broiler chicken age restriction caution statement from 10 days to 18 days.

C. Supplemental Applications

This supplemental NADA did not require a reevaluation of the safety or effectiveness data in the original NADA (21 CFR 514.106(b)(2)).

D. Patent Information:

For current information on patents, see the Animal Drugs @ FDA database or the Green Book on the FDA CVM internet website.